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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/776,910	02/06/2001	Robyn Joyce Russell	50179-087	3696

7590 12/04/2003

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EXAMINER	
RAO, MANJUNATH N	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 12/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/776,910	RUSSELL ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-12 and 14-29* is/are pending in the application.

4a) Of the above claim(s) *10-12 and 19-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9 and 14-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 9-12, 14-29 are still at issue and are present for examination. Claims 9, 14-18 are now under consideration. Claims 10-12, 19-29 remain withdrawn from consideration as being drawn to non-elected invention.

Claim Objections

Claim 18 is objected to because of the following informalities: Claim 18 recites the SEQ ID NO:10 as "4SEQ ID NO:10" which appears to be due to a typographical error. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 14 is unclear because claims 14-16 recites the limitation "wherein said DNA molecule" in line 2. There is insufficient antecedent basis for this limitation in the claim. Claim 9 on which claims 14-17 depend from is drawn to a recombinant enzyme capable of hydrolyzing a organophosphate wherein the enzyme has at least about 75% amino acid sequence identity with SEQ ID NO:8 and differs from SEQ ID NO:8 at least in the substitution of Trp at position 251 with an amino acid selected from the group consisting of Leu, Ser etc. There is no reference to nucleic acid molecule in the amended claim. Correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9, 13-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an enzyme with SEQ ID NO:8 and encoded by either SEQ ID NO:1, 3, or 5 and having a amino acid substitution at position 251, wherein the substituted amino acids are either Leu, Ser, Ala, Ile, Val, Thr, Cys, Met or Gly and capable of hydrolyzing organophosphates, does not reasonably provide enablement for any such enzyme having at least 75% homology to SEQ ID NO:8 and differing from SEQ ID NO:8 in having a amino acid substitution at position 251, wherein the substituted amino acids are either Leu, Ser, Ala, Ile, Val, Thr, Cys, Met or Gly. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 9, 13-17 are so broad as to encompass any organophosphate degrading enzyme having at least 75% amino acid sequence identity to SEQ ID NO:8 and differing from SEQ ID NO:8 in having a amino acid substitution at position 251, wherein the substituted amino acids are

either Leu, Ser, Ala, Ile, Val, Thr, Cys, Met or Gly. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of said enzymes broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only one said enzyme comprising the specific amino acid changes mentioned above. It would require undue experimentation of the skilled artisan to make and use the claimed polypeptides. The specification is limited to teaching the making and using amino acid sequence with SEQ ID NO:8 and differing from SEQ ID NO:8 in having a amino acid substitution at position 251, wherein the substituted amino acids are either Leu, Ser, Ala, Ile, Val, Thr, Cys, Met or Gly and wherein said polypeptide continues to have organophosphate hydrolyzing activity but provides no guidance with regard to the making of variants and mutants as claimed or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the

claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any organophosphate hydrolyzing enzyme encoded by polynucleotides SEQ ID NOS:1, 3, or 5 having an amino acid sequence identity to SEQ ID NO:8 and differing from SEQ ID NO:8 in having a amino acid substitution at position 251, wherein the substituted amino acids are either Leu, Ser, Ala, Ile, Val, Thr, Cys, Met or Gly, because the specification does not establish: (A) regions of the protein structure (except for the amino acid position 251) which may be modified without effecting activity; (B) the general tolerance of above enzymes to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope

of the claims broadly including enzymes having 75% amino acid sequence identity to SEQ ID NO:8 and differing from SEQ ID NO:8 in having a amino acid substitution at position 251, wherein the substituted amino acids are either Leu, Ser, Ala, Ile, Val, Thr, Cys, Met or Gly with an enormous number of amino acid modifications. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of enzymes having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Applicants argue that the rejection under 35 U.S.C. §112, first paragraph is not proper because the specification teaches three independent malathion resistant clones of *L.cuprina* genus and applicants have also isolated and characterized orthologous gene from housefly. Applicants argue that said polypeptide isolated from housefly shares 75% sequence identity with *L.cuprina* and refer the Examiner to Figure 2. Applicants argue that the present claims are drawn to polypeptides with 75% sequence identity with SEQ ID NO:8 and the specification shows sequence alignments and demonstrates the importance of residue 251. Applicants argue specification demonstrates to those skilled in the art that numerous amino acid substitutions can be made while retaining the claimed enzyme activity without undue experimentation, including conservative amino acid substitutions.

Examiner acknowledges that applicants have indeed provided resistant clones and isolated the polynucleotide sequence from house fly. Examiner also acknowledges that applicants provide the sequence alignment of the enzyme isolated from the house fly (SEQ ID

NO:8) and that of *L.cuprina* (SEQ ID NO:13) in figure 2. However, it should be noted that it is SEQ ID NO:8 that has 75% sequence identity to SEQ ID NO:13. Applicants are claiming a polypeptide that is 75% identical to SEQ ID NO:8 which is already 75% identical to SEQ ID NO:13. Therefore while those skilled in the art would probably know how to make changes to SEQ ID NO:13 using the above alignment, they would not know how to make further changes to a polypeptide that is already different from the reference molecule, i.e., SEQ ID NO:13. The specification lacks any teaching or guidance as to how those skilled in the art would be able to make changes to SEQ ID NO:8 without any undue experimentation.

In view of the above applicant's arguments are not persuasive because while methods to produce variants of a known sequence, such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan, producing variants as claimed by applicants requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the large number of variants have the claimed property. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute undue experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification. As previously stated the specification does not establish: (A) regions of the protein structure which may be modified without effecting activity; (B) the general tolerance of said enzymes to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue with an expectation of obtaining the desired biological

function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Hence the above rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 9, 13-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Whyard (a) et al. (Pesticide Biochemistry and Physiology, 1994, Vol. 50(3):198-206) or Whyard (b)et al. (Biochemical genetics, 1994, Vol. 32(1-2):9-24). This rejection is based upon the public availability of a printed publications. Claims 9, 13-18 are directed to enzyme capable of hydrolyzing an organophosphate that has at least 75% amino acid sequence identity to SEQ ID NO:8, wherein said recombinant enzyme differs from SEQ ID NO:8 at least in that the original amino acid Trp at position 251 is substituted with a Ser , Leu, ser, Ala, Ile, Val, Thr, Cys, Met or Gly. Whyard (a) and Whyard (b) references disclose the isolation and characterization of malathion carboxylesterases from *L.cuprina* strains that were resistant to the organophosphate insecticide. Because the claimed enzyme is functionally identical to that disclosed in the references and because applicants have not shown any material difference between the enzyme isolated by Whyard et al. and the recombinant form of the enzyme claimed, Examiner takes the position that the enzymes disclosed in the references and that claimed in the instant application are one and the same. With regard to the specific amino acid substitution claimed, Examiner takes the position that while the above references do not explicitly disclose the amino acid

sequence or disclose the method of obtaining the enzyme through recombinant techniques as claimed by the applicants, such characteristics of the enzyme are all inherent and applicants have not done any thing to the naturally produced enzyme except for determination of the amino acid sequence. Applicants have also not shown any specific characteristic that renders the recombinant enzyme as a distinct enzyme from the naturally occurring enzyme. Therefore, Whyard (a) or Whyard (b) et al. anticipate claims 9, 13- 18 as written.

Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

In response to the above rejection , applicants argue that neither prior art reference discloses the amino acid sequence or the nucleotide sequence and therefore neither reference anticipates the claimed recombinant enzyme. Applicants also argue that above references do not render the claim obvious either, even though Examiner had not made any obviousness rejection. However, as stated in the above rejection and in the previous rejection, Examiner continues to take the position that amino acid sequence information is inherent to polypeptides and therefore, contrary to applicant's argument, above references do anticipate the claims in question even though there is no amino acid sequence recitation in the claims. Hence the above rejection is maintained.

Conclusion

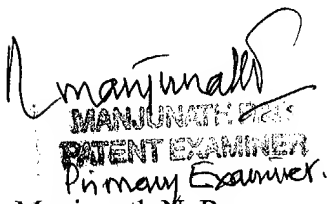
None of the claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 703-306-5681. The examiner can normally be reached on 7.30 a.m. to 4.00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-306-0196.



Manjunath N. Rao
November 26, 2003